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Children's Hospital of Pittsburgh and Diabetes Institute of the Walter Reed Health Care System Genetic Screening in Diabetes: Candidate Gene Analysis for Diabetic Retinopathy

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14. ABSTRACT
The hypothesis to be tested is that there are allelic variations of some genes that make the development of diabetes-related complications more likely in patients who carry them than those who do not. The 3 major complications to be evaluated are diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy. This is an observational study in which the investigators will obtain DNA samples from the blood of patients with one or more of these complications and from as many their first-degree relatives as possible for testing in the laboratory of Dr. Massimo Trucco is an internationally known immunologist and respected leader in genetic research in diabetes. He will evaluate these samples by studying candidate genes selected *a priori* and testing for transmission/disequilibrium – a standard for analysis of linkage between a candidate gene and a specific disease.

15. SUBJECT TERMS

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Introduction

Although deaths today from the acute effects of diabetes are rare, the associated vascular, retinal, neurological and renal complications are responsible for high levels of morbidity and mortality in diabetes. However, it has been observed that only a subset of diabetics appear to be susceptible to the development of diabetic complications, i.e., nephropathy, autonomic neuropathy, and retinopathy and there is data to suggest that there is a genetic component to this increased susceptibility. This investigation is testing the hypothesis that there are allelic variations of some genes that make the development of diabetes-related complications more likely in patients who carry them than in those who do not. Initial emphasis is on the examination of candidate gene analysis in families for diabetic nephropathy, autonomic neuropathy, and retinopathy.

Body

The title of this study is "Genetic Screening in Diabetes." This is an observational study in which COL Vigersky and his research team are obtaining DNA samples from the blood of patients with type 1 or 2 diabetes who have at least one of three diabetic complications (as specified in SF298) and from as many of their first-degree relatives as possible for genetic testing. The study is being performed at WRAMC for DEERS-eligible subjects and at the White Flint Professional Building in Kensington, Maryland for non-DEERS-eligible subjects. After meeting eligibility requirements, all subjects complete a medical history, a quality of life questionnaire, a physical examination, blood and urine sampling and analysis, and additional procedures to rule out diabetes and the presence or absence of the three diabetes-related complications that are being studied. All blood samples will be typed and examined to evaluate if there are reasonable candidate genes that contribute to the genetic susceptibility and/or development of diabetic nephropathy, neuropathy, and retinopathy. It is expected that WRAMC will enroll up to 100 probands and 300 of their family members.

Key Research Accomplishments

- After extensive revisions, the study was approved by the Clinical Investigation and Human Use Committees at WRAMC in March 2006 and the Clinical Investigation Research Office in April 2006.
- The protocol was approved by the Institutional Review Board (IRB) at USUHS in April 2007 to conduct the study on non-DEERS eligible relatives. The non-DEERS eligible subjects are currently being seen in the White Flint Professional Building, Suite 303, 11119 Rockville Pike, Kensington, MD. Dr. Kevin Leary was the Principal Investigator at USUHS from the time that the study was submitted and subsequently approved.

- Recruitment began on April 4, 2007.
- As of 22 April 2009, fifty five probands and fifty five family members have completed the study. Enrollment was suspended for 4 months (August-November 2008) due to a prolonged annual progress report review process by USUHS.
- The study manager function of the web-based Comprehensive Diabetes Management Program (CDMP) has been tailored to use to document all aspects of the protocol.
- Consistent with the study protocol, all subjects have had a physical examination, several noninvasive procedures to assess heart rhythm (electrocardiogram), retinopathy (retinal imaging), and diabetic autonomic neuropathy, as well as blood and urine sampling. First degree relatives who have not been diagnosed with diabetes receive an oral glucose tolerance test (OGTT) to determine if they have diabetes.
- Samples from the 110 consented subjects have been sent to the Rangos Research Center, University of Pittsburgh, Pittsburgh, PA for genetic analysis.
- Dr. Louis Pangaro assumed the role of the USUHS Principal Investigator when Dr. Kevin Leary is transferred in May 2008.
- MAJ Abel Alfonso was approved as the WRAMC Principal Investigator during COL Vigersky's deployment 01 March 08 through June 08. The approval letter re-instating COL Vigersky as PI was received by the DI on 25 Aug 2008
- Rangos Research Center will use data from our samples to confirm the findings from their studies regarding the association of specific genes to diabetic nephropathy.
- Additional funding to complete the enrollment goal of 100 probands and up to 300 first degree family members has been requested from Dr. Massimo Trucco.

Reportable Outcomes

- There are no findings to date from the samples we have sent to Rangos Research Center,

Plans

- The research staff will continue to aggressively recruit probands who have either type 1 or 2 diabetes with evidence of at least one of the microvascular complications of diabetes and at least one first degree relative who is available and consents to be in the study.
- In addition to referrals from Diabetes Institute nurse practitioners, endocrinologists, and diabetes educators, a description of the study and contact information is posted on the DI website, is in the quarterly DI newsletter, and is included in the handout material given to the patients attending the diabetes self management classes. Information about is also provided at health fairs at WRAMC and the satellite MTFs. Study flyers will be sent electronically and periodic visits will be made to ophthalmologists, optometrists, nephrologists, and primary care providers in the WRHCS. Lastly, during normal clinic

operation (0800-1630) we plan to describe current DI studies in a 3 to 5 minute spot that will be shown once every hour on WRAMC closed circuit TV (CCTV).

Conclusions

There are no conclusions from our data to date.

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Appendices

Appendix A: Candidate genes for Diabetic Complications (see legend)

EXTRACELLULAR MATRIX	SYMBOL	CHROMOSOME
collagen 4A1	COL4A1	13q34
collagen 4A2	COL4A2	13q35
collagen 4A3	COL4A3	2q36-q37
collagen 4A4	COL4A4	2q36-37
collagen 4A5	COL4A5	Xq22
collagen 4A6	COL4A6	Xq22
fibronectin 1	FN1	2q34
integrin, alpha 2	ITGA2	5q23-q31
integrin, alpha V	TGA5	12q11-q13
integrin, beta 1	ITGB1	10p11.2
laminin A4	LAMA4	6q21
laminin B1	LAMB1	7q22
laminin B2	LAMB2	3p21.1
nidogen (entactin)	NID	1q43
ENZYMES		
#aldose reductase	ALDR	7q35
*angiotensin converting enzyme	ACE	17q23
cathepsin B	CTSB	8p22
endothelin converting enzyme 1	ECE-1	1p36.1
metalloproteinase-3 (stromelysin)	MMP3	11q23
*methylenetetrahydrofolate reductase	MTHFR	1p36.2
*paraoxonase 1	PON1	7q21.1
protein kinase C, alpha	PRKCA	17q22-q23.2
protein kinase C, beta 1	PRKCB	16p11.2
renin	REN	1q32
tissue inhibitor of metalloproteinase 2	TIMP-2	17q25
tissue inhibitor of metalloproteinase 3	TIMP-3	22q12.1-q13.2
CYTOKINES & GROWTH FACTORS		
fibroblast growth factor 2 (basic)	FGF2	4q25-q27
insulin-like growth factor 1	IGF1	12q22-q24.1
insulin-like growth factor binding protein-1	IGFBP1	7p14-p12
platelet-derived growth factor beta	PDGFB	22q12.3-q13.1

transforming growth factor-beta1	TGFB1	19q13.1-q13.3
transforming growth factor-beta2	TGFB2	1q41
transforming growth factor-beta3	TGFB3	14q24
*vascular endothelial growth factor	VEGF	6p21.1

HORMONES

atrial natriuretic factor (peptide)	NPPA	1p32.6
adrenomedullin	M	11
angiotensinogen	AGT	1q42-q43
preproendothelin	EDN1	6p24-p23

RECEPTORS

AGE receptor	AGER	6p21.3
angiotensin-2 receptor 1A	AT2R1	3q21-q25
*beta-adrenergic receptor	ADRB2	5q31.1-qter
endothelin receptor A	EDNRA	12q22.1
endothelin receptor B	EDNRB	13q22
insulin-like growth factor 1 receptor	IGF1R	15q25-q26
insulin receptor-related receptor	INSRR	1q21-q22
PDGF receptor-beta	PDGFRB	5q31-q32
#Toll-like receptor 4	TLR4	
transforming growth factor-beta receptor II	TGFBR2	3p22
transforming growth factor-beta receptor III	TGFBR3	1p33-p32
#tumor necrosis factor receptor 4	TNFRSF1B	1p36

TRANSCRIPTION FACTORS

c-fos	FOS	14q24.3
c-jun	JUN	1p32-p31
c-myc	MYC	8q24.1-q24.13

OTHERS

apolipoprotein-E	APOE	19q13.2
glucose transporter-1; solute carrier family 2	GLUT1, SCL2A1	1p35-p31.3
Na+/H+ antiporter; solute carrier family 9	NHE1; SLC9A1	1p36.1-p35

Legend:

* Signifies candidate gene for retinopathy
# Signifies candidate gene for neuropathy
All others are candidate genes for nephropathy

Supporting Data

The information and new technology generated by the Human Genome Project are making it possible to perform large-scale, comprehensive, gene expression analyses. Technical advances in DNA microarray have made it possible to study hundreds to thousands of transcripts simultaneously. The identity and function of many transcripts are already available in public database such as dbEST and Unigene. Together, these advances should allow a different approach to studying the genetic basis of complex diseases. Instead of starting from genetic variation detected at the DNA level, and then determining whether that variation plays a role in gene expression and protein function, we can also study the gene expression pattern, then look for the genetic variation.